

# NIH Centers of Excellence

## Rare Diseases Clinical Research Network

### Overview

#### Why the RDCRN Was Established

The need for centers of excellence for rare diseases research has been voiced for more than 20 years. A disease is defined as rare if fewer than 200,000 persons in the United States have it. Scientists have identified approximately 6,500 rare diseases and believe that approximately 80 percent have a genetic origin.

In 1989, the National Commission on Orphan Diseases considered the lack of specialized centers for the diagnosis and treatment of rare diseases to be a serious barrier to the advancement of research on rare diseases. The commission found that 15 percent of patients with rare diseases had to wait 5 years or more to obtain a correct diagnosis. An additional 30 percent of patients waited 1 to 5 years before obtaining a diagnosis.

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In 1999, the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research endorsed the need for specialized centers for rare diseases. The panel recommended funding for specialized research and diagnostic centers for major categories of rare diseases. The panel recommended establishing rare diseases centers of excellence on a graduated basis, starting with 10 regional centers in the first year with incremental increases of 10 centers per year until NIH had established 40 regional centers. The panel also emphasized that centers should work closely with patient advocacy groups. Congress realized the panel's recommendations with the Rare Diseases Act of 2002, Pub. L. No. 107-280. In response to the Act, NIH established the Rare Diseases Clinical Research Network (RDCRN) in 2003. ORDR partnered with 6 NIH ICs to fund 10 RDCRN consortia that focused on rare disease groups at multiple academic institutions and shared a central Data and Technology Coordinating Center (DTCC).

In February 2008, ORDR, in collaboration with several NIH ICs, released two RFAs to recompute the network and establish Phase II of the RDCRN—[Rare Diseases Clinical Research Consortia \(RDCRC\) for the Rare Disease Clinical Research Network \[U54\]](#) (RFA-OD-08-001) and [Data Management and Coordinating Center \(DMCC\) for the Rare Diseases Clinical Research Network \[U54\]](#) (RFA-OD-08-002). Existing as well as potentially new consortia and data coordinating centers were invited to apply.

ORDR and 7 NIH Institutes funded and provided administrative support to 19 consortia and the DMCC (see Table 4-5) in FY 2009. These Phase II RDCRN awards are for 5 years.

#### How the RDCRN Functions within the NIH Framework

In 2009, the RDCRN grew from 10 to 19 consortia, 4 of which were funded through the American

Recovery and Reinvestment Act (ARRA).

Originally, in Phase I, ORDR partnered with six NIH Institutes (NCRR, NICHD, NINDS, NIAMS, NIDDK, and NHLBI) in administering and funding the network. For Phase II of the network, ORDR is partnering with seven Institutes: NICHD, NIAMS, NINDS, NHLBI, the NIAID, NIDDK, and NIDCR.

Each consortium develops clinical protocols for a set of related rare diseases and includes several participating institutions. The network incorporates uniform data and methodological standards across all the consortia and their component sites. The original RDCRN contained more than 70 sites across the United States and in other countries. The current network includes approximately 165 sites in at least 29 states. Twenty sites are in other countries. The total number of sites is expected to further facilitate enrollment of and access for patients.

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A steering committee guides the network. The steering committee consists of the principal investigator of each consortium, NIH representatives, and a patient advocacy representative nominated by the 57 collaborating patient advocacy groups. The patient advocacy groups associated with each consortium have formed a coordinating committee that is instrumental in participating in the development of informed consent statements, informational materials about diseases and treatments, protocols, recruitment strategies, and other important activities. Other network committees and working groups facilitate communication and collaboration across and within consortia to ensure research efficiency and excellence.

In general, the current network's infrastructure and functions build on lessons learned and uses those approaches that have proven to be most efficacious.

### **Description of Diseases and Conditions under Study in Phase II of the RDCRN**

With establishment of Phase II of the RDCRN, network researchers are poised to study 92 rare diseases, including:

*Urea cycle disorders (UCD):* UCDs are a group of genetic disorders caused by a deficiency of one of the enzymes in the urea cycle, which is responsible for removing ammonia from the blood stream. Because many cases of UCD remain undiagnosed, infants born with the disorders may die without a definitive diagnosis.

*Vasculitides:* Vasculitides are a heterogeneous group of diseases resulting in severe inflammation of blood vessels. Arteries and veins of any size in any organ may be affected, leading to damage to organs caused by a loss of the blood supply, known as ischemia.

*Genetic Disorders of Mucociliary Clearance:* Genetic disorders of mucociliary clearance include disorders such as primary ciliary dyskinesia (PCD), variant cystic fibrosis (CF), and pseudohypoaldosteronism (PHA). They reflect genetic defects in airway host-defense and impaired clearance of mucus, and typically result in severe chronic infection of the airways.

*Dystonias:* The dystonias are a group of neurological disorders characterized by involuntary twisting movements and unnatural posturing. Focal dystonias affect only one body part. Some of the most common forms of focal dystonia are cervical dystonia, affecting the neck; blepharospasm, affecting the

eyelids; spasmodic (or laryngeal) dysphonia, affecting the voice box; craniofacial dystonia, affecting the lower face; and limb dystonias, affecting the hand or arm or foot or leg.

*Brain vascular malformations:* Brain vascular malformations are characterized by veins and blood vessels in the brain that are structurally malformed and can cause drainage of an area of the brain, resulting in repeated and debilitating bleeding, seizures, and hemorrhaging as a result of the formation of blood clots. Brain vascular malformations are resource-intensive to manage effectively, and have high probability of serious neurological morbidity. Specific medical therapies for these diseases are lacking.

*Immune-Mediated Disorders Post Transplant of Donor Bone Marrow:* Hematopoietic stem cell transplantation is the infusion of stem cells from the bone marrow of a donor into a patient to treat tumors, disorders of the blood, immunodeficiency syndromes, congenital enzyme deficiencies, and autoimmune disorders. Persons who receive grafts from donors (known as allogeneic or allografts) are at a substantially greater risk for graft-versus-host disease and delayed immune system recovery than are persons who receive grafts harvested from one location on their body and transplanted to another site (autografts). Recipients of allografts also have greater rates of graft rejection, cytomegalovirus infection, invasive fungal infection, and Epstein-Barr virus-associated post-transplant lymphoproliferative disease, in which the body has too many white blood cells, which can overactivate the immune system.

*Nephrotic Syndromes or Nephrosis:* Nephrotic syndromes and nephrosis cause damage to the kidney, resulting in leakage of large amounts of protein into the urine. The loss of so much protein in the kidney causes other conditions, which are often characterized by excess body fluid.

*Primary Immune Deficiencies:* Primary immune deficiencies, also called primary immune disorders, weaken the immune system, allowing repeated infections to occur more easily. Many people with primary immunodeficiency are born without some of the body's immune defenses, which leaves them more susceptible to infections. In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly.

*Lysosomal Storage Diseases:* Lysosomal storage diseases are a large group of diseases, each characterized by a specific lysosomal enzyme deficiency in a variety of tissues. Consortium investigators study 11 lysosomal storage diseases—mucopolysaccharidoses (MPS), Batten disease, Niemann-Pick disease type C, mucopolipidosis type IV, late infantile neuronal ceroid lipofuscinosis, glycoproteinosis, Wolman disease, Pompe disease, bone disease in the MPS, and Fabry disease. These conditions involve severe central nervous system disease, which is difficult to treat. They are devastating to quality of life and can lead to dementia and death.

*Autonomic Rare Diseases:* The autonomic nervous system controls vital involuntary body functions, such as blood pressure; heart and breathing rates; body temperature; digestion; metabolism; the balance of water and electrolytes; the production of saliva, sweat, and tears; urination; defecation; and sexual response. Disorders of the autonomic nervous system can affect any body part and may be reversible or progressive.

*Charcot Marie Tooth Disease (CMT):* CMT is an inherited disease involving damage to the nervous system. Even patients with this progressive disease who come from the same family show a wide range of symptoms. For example, progressive muscle wasting leads to problems with walking, running, and balance. Later in the course of the disease, hand function may become affected. Loss of nerve function in the extremities also can result in sensory loss. People can be unaware of having developed ulcers of the feet or of cuts or burns on the hands. Sensory loss can lead to gradual hearing impairment and, sometimes, deafness. Some people with CMT also have tremors, usually of the hands. Weakness of the respiratory muscles can cause life-threatening problems. Scoliosis of the spine also is associated with this disease. No effective therapies are available for any form of CMT.

*Hereditary Nephrolithiasis and Kidney Failure:* Hereditary causes of nephrolithiasis and kidney failure are

inborn errors of metabolism that lead to high concentrations of insoluble mineral salts in the urine and severe, recurrent kidney stones. Patients with primary hyperoxaluria (PH), cystinuria, adenine phosphoribosyltransferase deficiency (dihydroxyadeninuria [DMA]), and Dent disease experience stones beginning in childhood. All patients with hereditary nephrolithiasis and kidney failure experience deposition of crystals in kidney tissue and loss of kidney function. Disease expression varies widely. Some PH patients progress to end-stage renal failure during infancy. Progress toward effective treatment has been slow.

*Porphyrias:* Porphyrias are a group of inherited metabolic disorders that arise as a result of a malfunction in one of the eight steps in the body's synthesis of a complex molecule called "heme," which is essential for the transport of oxygen to cells in the body. A common feature of all porphyrias is the accumulation in the body of porphyrins, chemicals that are normally present in the body but do not normally accumulate, or porphyrin precursors. The type of porphyria depends on which of these chemicals builds up. Symptoms include effects on the nervous system and burning, blistering, and scarring of sun-exposed areas of the skin.

*Angelman, Rett, and Prader-Willi Syndromes:* Angelman syndrome is a complex genetic disorder that primarily affects the nervous system and causes developmental delay, intellectual disabilities, severe speech impairment, seizures, small head size, and problems with movement and balance in young children. Rett syndrome is a childhood neurodevelopmental disorder characterized by normal early development followed by loss of purposeful use of the hands, distinctive hand movements, slowed brain and head growth, gait abnormalities, seizures, and intellectual disabilities. Prader-Willi Syndrome (PWS) is a rare genetic disorder that causes poor muscle tone, low levels of sex hormones, and a constant feeling of hunger.

*Sterol and Isoprenoid Disease:* Sterol and isoprenoid diseases are a group of rare diseases bound by common biochemistry and severe impact on health: cerebrotendinous xanthomatosis (CTX), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), Niemann-Pick disease type C (NPC), sitosterolemia, Sjogren-Larsson syndrome (SLS), and Smith-Lemli-Opitz syndrome (SLOS).

*Salivary Gland Carcinomas:* Salivary gland carcinomas are comprised of widely varied subtypes with different clinical behaviors and can result in disfigurement, death, or both. In general, salivary gland carcinomas afflict individuals later in life. The cause of salivary gland tumors remains unknown. Of the risk factors investigated, exposure to radiation has been the only known factor associated with salivary gland tumors. Individual differences in sensitivity to radiation have been implicated as an underlying cause for the development of these tumors.

*Inherited Spinocerebellar Ataxias:* Inherited forms of spinocerebellar ataxias 1, 2, 3, and 6 are a heterogeneous group of disorders characterized by degenerative symptoms in the cerebellum, spinal cord, and brain stem. Ataxia means "loss of the ability to coordinate muscular movement." Degenerative ataxias show continuous worsening of the disease, leading to severe disability or death. Currently, there are no treatments for these disorders.

*Neurologic Channelopathies:* Nervous system channelopathies include episodic ataxias, non-dystrophic myotonic disorders, and Andersen-Tawil syndrome. The episodic ataxias are characterized by attacks of clumsiness and imbalance triggered by factors such as stress or fatigue. Episodic ataxia type 1 is characterized by episodes of imbalance with fine twitching or rippling of muscles, which is difficult to see except in small muscles of the hands and face. Episodic ataxia type 2 is characterized by episodes of slurring of speech, gait imbalance, and dysfunction of eye movements. The non-dystrophic myotonias are a very rare group of muscle disorders caused by abnormalities in different muscle cell membrane proteins. Patients experience impaired muscle relaxation that causes impaired physical activity, pain, and weakness. There are no proven therapies, and it is not known if treatment should differ for different disease subtypes. Andersen-Tawil syndrome is a rare form of periodic paralysis that affects the function

of skeletal and heart muscles. Periodic paralysis is characterized by episodes of muscle weakness.

*Respiratory Chain Mitochondrial Diseases:* Mitochondrial diseases due to defects of the respiratory chain are clinically and genetically diverse; occur most often in infants, children, and young adults; and can be fatal. (Mitochondria are units within cells that generate its energy. The “respiratory chain” is the process by which mitochondria generate potential energy). Diagnosis of respiratory chain mitochondrial disease is difficult because of the broad variability in symptoms. Many of these diseases progress rapidly, and no treatments currently exist. The common link that these diseases share is the inability of the mitochondria to completely burn food and oxygen, a critical function for the mitochondria to generate the energy needed by cells to function properly. Mitochondrial impairment results in a host of devastating conditions, including respiratory chain diseases with complex clinical features, such as neurological and muscular dysfunction often accompanied by kidney dysfunction, hormone, cardiac, and liver complications.

More information on these rare diseases is available in the NIH Rare Diseases and Related Terms glossary at <http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1>.

## **Burden of Illness**

The burden of illness for all rare diseases is difficult to assess because of the large number of disorders, the complexity of each disease, and the limited availability of prevalence and incidence data. The National Organization for Rare Disorders (NORD) estimates that 25-30 million people in the United States have a rare disease.

Overall, rare diseases are devastating and costly. This is due partly because of their severity and partly because diagnosis can take a long time, often occurring well after symptoms have appeared. In addition, often treatment is not available once a disease is diagnosed. Moreover, scientists cannot assess the pain, suffering, and lost opportunities experienced by patients and their families.

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## **Scope of NIH Activities: Research and Programmatic**

The RDCRN brings together experts who are skilled in studying, diagnosing, and treating particular groups of rare diseases and who are eager to train junior faculty and postgraduate fellows. In addition, the network enables each consortium to gather groups of patients with similar or related disorders, fosters basic scientific investigation and longitudinal natural history and epidemiological studies, encourages synergy in translational research, and enhances opportunities for collaborative clinical investigation. The 2003-2008 DTCC and the current DMCC enable sharing of study results nationally and internationally in a timely and uniform way. Although the DMCC has primary responsibility for the coordination and management of data, participating RDCRN institutions, NIH program officers, and patient advocacy group representatives provide input and participate actively in overall data coordination.

## **NIH Funding for FY 2008 and FY 2009**

Actual NIH funding for the RDCRN in FY 2008 was \$10.2 million for 10 consortia and the DTCC. In FY

2009, actual funding for the 19 consortia and the DMCC was \$23.4 million, including \$2.1 million from ARRA funds. The total cost over 5 years for the RDCRN's Phase II is estimated to be \$117 million.

## FY 2008 and FY 2009 Progress Report

### Programmatic and Research Activities and Outcomes

Throughout its first funding cycle, the RDCRN cumulatively enrolled more than 5,500 patients in 37 clinical studies. Patient recruitment for clinical studies is a fundamental challenge in rare diseases research because typically there are few affected patients in any one geographic area. The RDCRN is designed to address this problem by fostering collaboration among scientists and sites and shared access to geographically distributed research resources.

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The Coalition of Patient Advocacy Groups included representatives of 57 patient advocacy groups by late 2009. The coalition assists in many aspects of network research and publications. The protocols ranged from natural history studies to research on biomarkers, treatment efficacy, and genotype-phenotype correlations; genetic analyses; Phase I and II clinical trials; and pilot projects.

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*The Rare Diseases Clinical Research Network benefits from a coalition of patient advocacy groups that grew to 57 in 2009. The coalition assists in many aspects of network research and the development of educational materials.*

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The RDCRN is unique in its approach to addressing rare diseases as a group. Previously, the NIH ICs funded research on individual rare diseases in their respective disease-type or organ domain. The network established a comprehensive training program for clinical investigators and developed a network-wide website to inform the public, physicians, patients, and investigators about the rare diseases under study. The network's aims continue to include training a cadre of young investigators in the clinical, pathophysiologic (physiological process associated with disease), and pharmacologic aspects of specific rare diseases. The network's training includes instruction on and experience with methodologies for patient-oriented clinical research in rare diseases, including biostatistics and epidemiology; and the conceptualization, ethics, design, implementation, analysis, and reporting of controlled clinical trials. An integrated training program provides supervision by clinicians and biostatisticians with extensive experience in investigating rare diseases and developing novel therapies. The training program also provides an integrated statistics, epidemiology, and computer science curriculum; seminars on clinical trial design; courses in the basic sciences underlying experimental therapeutics and in ethics; career development support; participation and collaboration with network faculty with expertise in designing rare diseases studies; clinical experience in intensively investigating disease states; and mentoring to achieve an independent academic career in rare diseases.

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*The Data and Technology Coordinating Center created a central public website, developed as a portal for the rare diseases community, including patients and their families and health care professionals. The website provides information on rare diseases research, consortium activities, approved protocols,*

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*disease information, and practice guidelines. The website had more than 3.4 million visits in 2008.*

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The RDCRN is the first program that aims to create a specialized infrastructure to support rare diseases research. The DTCC developed and enabled new technologies, tools, and services for the network. These tools and services included electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, website development and maintenance, and database-querying tools. The DTCC, in collaboration with each consortium, also implemented an effective patient contact registry that allows individuals to register to receive information about new or ongoing clinical studies in addition to periodic educational updates and to consider participating in clinical studies. To facilitate patients' transportation to RDCRN sites, Angelflight NIH links patients with volunteer pilots who donate their time, planes, fuel, and operating expenses to transport patients and family members free of charge. By accepting donated frequent flyer miles, Angelflight also provides free tickets from select commercial airlines. The goal of the program is to ensure that no patient is denied access to medical evaluation or ongoing research projects because of a lack of air transportation.

## Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN

In 2008, ORDR and participating NIH program staff reviewed the RDCRN's progress before publishing two RFAs. As a result of this review, ORDR staff decided to open the RFAs to the incumbent consortia and the DTCC as well as to new applicants. Some consortia were not renewed and many new consortia were added to the network.

ORDR and NCRR convened a workshop on July 16, 2009, titled "Advancing Rare Diseases Research through Networks and Collaboration." The workshop featured several speakers from the RDCRN and addressed the advantages and occasional disadvantages of multicenter collaborations in rare diseases research, trainee experiences, patient recruitment, outreach and dissemination, strategies for forming effective teams and networks, the interplay of basic and clinical research in the translation process, and the application of clinical research findings to clinical practice. Suggestions for improvements from workshop speakers included further increasing the number of sites in each consortium, even if this increase could result in fewer participants per site, and including more biostatisticians with expertise in small patient populations early in protocol development at participating institutions in addition to central technical support from the DMCC.

### Evaluation Plans

Because the RDCRN has been in operation only since 2003, it has not yet been formally evaluated to assess the impact of its research and training activities. Until that is possible, NIH will continue to regularly review RDCRN performance via scrutiny of progress reports, site visits, and program reviews.

When the RDCRN's impact on research and its contribution to rare diseases treatment is more mature and measurable, the RDCRN's contribution to the health of the Nation will be determined using the following criteria:

- Study completion and outcomes
- Timely recruitment of adequate patient populations
- Number of trainees who complete their training programs
- Trainees' impact on the rare disease field

- Impact of scientific publications on future rare diseases research
- Contribution of the DTCC and subsequent DMCC to research in the form of a coordinated data management system; the ability to capture and integrate many different types of data; and the development and broad acceptance of novel technological approaches to distributed computing, federated databases, and data mining within and across diseases.

## Future Directions

ORDR and its partner Institutes will continue to work with the RDCRN and encourage the continued training of new rare diseases researchers. The current consortia and the DMCC will build on the experience and lessons learned in the program's previous years. ORDR hopes that in response to the recommendations of the 1999 NIH Special Emphasis Panel on the Coordination of Rare Diseases Research, the numbers of consortia, sites in each consortium, trainees, and patients served will continue to increase in the United States and in other countries. As a result, patients and their families will be able to look forward to better treatments and cures, improving the duration and quality of their lives.

**Table 4-5. Rare Diseases Clinical Research Network**

Institution and Location	Year Established
Boston University School of Medicine, Boston, MA	2003
Children's National Medical Center, Children's Research Institute, UCDC, Washington DC	2003
University of Alabama at Birmingham, AL (previously Baylor College of Medicine, Houston, TX)	2003
University of Rochester, NY	2003
University of South Florida, Tampa, FL (DMCC)	2003
University of North Carolina, Chapel Hill, NC	2004
Columbia University Medical Center, New York, NY	2009
Emory University, Atlanta, GA	2009
Fred Hutchinson Cancer Research Center, Seattle, WA	2009



Mayo Clinic College of Medicine, Rochester, MN	2009
Mount Sinai School of Medicine of NYU, New York, NY	2009
Oregon Health and Sciences University, Portland, OR	2009
University of California, San Francisco, CA	2009
University of Florida, Gainesville, FL	2009
University of Michigan at Ann Arbor, MI	2009
University of Minnesota Twin Cities, Minneapolis-St. Paul, MN	2009
University of Texas MD Anderson Cancer Center, Houston, TX	2009
Vanderbilt University Medical Center, Nashville, TN	2009
Wayne State University, Detroit, MI	2009